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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,198	11/30/2000	Pierre L. Triozzi	CIR 2-005	2840

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,198	TRIOZZI ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 57-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 57-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 7, 2003 has been entered. The amendments submitted August 6, 2003 have been entered as requested in the RCE filing.

A petition to revive the instant application was granted on December 30, 2003 by the Office of Petitions.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

The rejection of Claims 1-8 and 57-66 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 12, 14, 17 and 18 of U.S. Patent No. 6,093,381 **is maintained** for reason of record. The rejection is evidenced by Triozzi et al. (AIDS Research and Human Retrovirus, 1998).

Applicants arguments are that the presence of components less than 50 kDa is detrimental to the activity of the factor. Applicants have chosen to (1) exclude the components of factors less than 50 kDa, and (2) the use of the factors greater than 50 kDa resulted in superior results. Applicants arguments are not convincing because the supernatant in the U.S. Patent No. 6,093,381can be shown by the Triozzi et al. (AIDS Research and Human Retrovirus, 1998) to

contain the IL12 and TNF-α mRNA expressed products. Furthermore, Il-12 has been purified because the sequence is known.

In response purified product may be considered new for the purpose of meeting 101 requirements, they may never the less be unpatentable for lack of invention as being obvious under 103. See *In Re Bergstom and Sjovall*, 166 USPQ 256 (CCPA 1970)

The instant invention is drawn to a product (a factor). The product-by-process claims are interpreted as "a composition of matter" (which are *products*, wherein the chemical nature of the substances or materials used. A composition may be a molecule, compound, solution, mixture, alloy, atom, etc.). Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed at treating a patient afflicted with a disease - cancer- comprising a greater than 50 kDa fraction of a supernatant from mitogenically stimulated lymph node lymphocytes. The factor is obtained from cells stimulated with IL-2 and anti-CD-3 Ab. The patented claims are drawn to a whole supernatant fraction from lymph node cells stimulated with IL-2 and anti-CD-3 Ab. The patented claims are drawn to improving the treatment of cancer patients utilizing this supernatant which inherently contains the greater than 50 kDa fraction. The limitation of "treating patients" is broad and includes combination therapies as found in claims 11, 12, 14, 17 and 18 of U.S. Patent No. 6,093,381. Triozzi et al. (AIDS Research and Human Retrovirus, 1998) teaches that mRNA is expressed in lymph node cells that have been treated with IL2 and anti-CD3 antibody, like the lymphocytes in U.S. Patent No. 6,093,381. IL12 and TNF-α mRNA is expressed in these treated cells. IL-12 is a

heterodimer protein with a molecular mass of 57.2 kDa in unglycosylated from and 75 kDa in glycosylated form. TNF-α is a multimeric protein that forms timers, the single unit of TNF is approximately 17 kDa in size and the trimer is approximately 51 kDa in size. Therefore, the instant rejection is maintained.

Claim Rejections - 35 USC § 102

The rejection of claims 1-8 and 57-66 under 35 U.S.C. 102(a) or 35 U.S.C. 102(e) as being anticipated by Triozzi et al. (U.S. Pat. No. 6,093,381) **is maintained** for reasons of record. The rejection is evidenced by Triozzi et al. (AIDS Research and Human Retrovirus, 1998).

Applicants arguments are that the presence of components less than 50 kDa is detrimental to the activity of the factor. Applicants have chosen to (1) exclude the components of factors less than 50 kDa, and (2) the use of the factors greater than 50 kDa resulted in superior results. Applicants arguments are not convincing because the supernatant in the U.S. Patent No. 6,093,381can be shown by the Triozzi et al. (AIDS Research and Human Retrovirus, 1998) to contain the IL12 and TNF-α mRNA expressed products. Furthermore, Il-12 has been purified because the sequence is known.

The claims are directed at lymphocytes derived from lymph node or peripheral blood. There is not objective evidence on the record that these cell populations actually behave differently in response to IL-2 and anti-CD3 treatment.

Triozzi et al. (AIDS Research and Human Retrovirus, 1998) teaches that mRNA is expressed in lymph node cells that have been treated with IL2 and anti-CD3 antibody, like the lymphocytes in U.S. Patent No. 6,093,381. IL12 and TNF-α mRNA is expressed in these

treated cells. IL-12 is a heterodimer protein with a molecular mass of 57.2 kDa in unglycosylated from and 75 kDa in glycosylated form. TNF-α is a multimeric protein that forms timers, the single unit of TNF is approximately 17 kDa in size and the trimer is approximately 51 kDa in size. Therefore, the instant rejection is maintained.

The rejection of claims 1, 5, 57 and 61 under 35 U.S.C. 102(b) as being anticipated by Chang et al. (U.S. Pat. No. 4,596,774) **is maintained** for reasons of record.

Applicant's response has been fully considered but is not deemed persuasive for the reason set out in the previous rejection. Applicant's arguments essentially are that the claims are limited to the process steps leading to the greater than 50 kDa fraction. However, the amendments are drawn to a product (a factor) made by a process. The amended claims does not distinguish over the prior art (Change et al.), which fractionated (isolated) the supernatant of stimulated cells on an SDS page gel (see figure 5). Thus the reference teaches an isolated factor (a composition) that is greater than 50 kDa in size on SDS-Page gel. Chang et al. disclose the methods of preparing cell-free products (supernatant) from stimulated peripheral blood lymphocytes. The supernatant contains all molecular weight fractions including those that are greater than or equal to 50 kDa (see figure 5). The reference discloses using the supernatant as a treatment. Therefore, the rejection is maintained.

The rejection of claims 1-8 and 57-66 under 35 U.S.C. 102(b) as being anticipated by Triozzi et al. (AIDS Research and Human Retrovirus, 1998) **is maintained** for reason of record.

Applicants arguments are that the presence of components less than 50 kDa is detrimental to the activity of the factor. Applicants have chosen to (1) exclude the components of factors less than 50 kDa, and (2) the use of the factors greater than 50 kDa resulted in superior results. Applicants arguments are not convincing because the supernatant of Triozzi et al. contains the IL12 and TNF-α mRNA expressed products. Furthermore, Il-12 has been purified because the sequence is known.

The claims are directed at lymphocytes derived from lymph node or peripheral blood. There is not objective evidence on the record that these cell populations actually behave differently in response to IL-2 and anti-CD3 treatment.

The rejection is maintained because the reference discloses that mRNA is expressed in lymph node cells that have been treated with IL2 and anti-CD3 antibody. IL12 and TNF-α mRNA is expressed in these treated cells. IL-12 is a heterodimer protein with a molecular mass of 57.2 kDa in unglycosylated from and 75 kDa in glycosylated form. TNF-α is a multimeric protein that forms timers, The single unit of TNF is approximately 17 kDa in size and the trimer is approximately 51 kDa in size. Thus, the instant reference anticipates the instant invention.

The rejection of claims 1-8, 57-66 under 35 U.S.C. 102(b) as being anticipated by Tanaka et al. (EMBO Journal, 1995) **is now reinstated**, although in a prior response to an office action Applicant's argument was that the specification has specifically pointed out that sFasL is not an active component of the factor. The claims as written do not specifically exclude the sFasL component. Thus the claims still read on sFasL. Applicant may amend the claims to specifically

exclude sFasL provided there is written description in the specification for the negative limitation.

The claims are directed at lymphocytes derived from lymph node or peripheral blood. There is not objective evidence on the record that these cell populations actually behave differently in response to IL-2 and anti-CD3 treatment.

Tanaka et al. disclose mitogen stimulated peripheral blood T lymphocytes for preparing a cell-free product: sFasL. The reference discloses that sFasL forms trimers and therefore achieves a size greater than the monomeric 40 kDa membrane form (greater than 50Kda). FasL association with Fas results in the activation of apoptosis leading to cell death and any cell that caries Fas is susceptible to this death pathway. Therefore, the instant invention is anticipated by Tanaka et al.

New rejections:

Claims 1, 2, 5, 6, 57, 58, 61 and 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Mire-Sluis et al. (Cytokines, 1998, pp. 183-203, 217-219, 227-230, 245-260, 277-296, 335-360, 526-546).

The instant invention is drawn to a product (a factor). The product-by-process claims are interpreted as "a composition of matter" (which are *products*, wherein the chemical nature of the substances or materials used. A composition may be a molecule, compound, solution, mixture, alloy, atom, etc.). Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. M.P.E.P. Section 2113 states that:

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The

> patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

The claims are directed at lymphocytes derived from lymph node or peripheral blood. There is no objective evidence on the record that these cell populations actually behave differently. Thus if a composition has been purified in one type of lymphocyte it is presumed to be present in the other type of lymphocyte as well.

Mire-Sluis et al. disclose IL-12 that is a heterodimeric protein. The protein backbone has a molecular mass of 57.2, although the glycosylated protein approximately 70 kDa as determined by analytical ultracentrifugation (see page, 186, 189, 532).

The reference discloses IL-14 which has a molecular mass of 53.1 kDa and is produced by normal T-cell, T cell clones and T cell lineage as well as B-cell lineage lymphoma cell lines (see page 218, 533).

The reference discloses IL-16 is a homotetramer having a molecular mass 56 kDa (see page 227, 534).

The reference discloses MCSF has a molecular mass of 45-90 kDa and is derived from T-cells (see page 247, 249, 537).

The reference LIF has an apparent molecular mass of 32-67, the LIF is produced and secreted by a wide variety of cells upon stimulation (see pages 278, 280, 238).

The reference teaches TNF and lymphotoxin (LF). The TNF and LF subunits have a molecular mass of 17 kDa and 25 kDa. TNF and LF form homotrimers that have a molecular

mass 51 kDa and 75 kDa. Trimers are the biologically active form of TNF and LF. (see pages 339, 340, 541)

Therefore, the instant invention is anticipated by Mire-Sluis et al.

Claims 1-8 and 57-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-8 and 57-66 are indefinite in that they only describe the compositions of interest by an arbitrary name (a factor). Here applicants are claiming a composition (a factor) by claiming the composition as a particular fraction of the supernatant of an activated lymphocyte. While the name itself may have some notion of the activity of the protein, there is nothing in the claims that distinctly claims the factor. For example, others in the field may isolate the same protein (factor) and have giving the protein such an entirely different name (e.g.,IL12, IL16, MCSF, TNF, LF, sFasL). Applicant should particularly point out and distinctly claim the composition by claiming characteristics associated with the factor (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Here Applicants are attempting to narrow the supernatant fraction to only claiming those proteins in the fraction that comprise compositions greater that 50 kDa, however, the prior art has shown that lymphocyte produce many cytokines that may fall within the claimed factor and they have not sufficiently defined their composition from those in the prior art. Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of. In consideration of the discrepancies often encountered in the art between protein molecular weight when

determined by different methods, when a molecular weight is recited to characterize a protein (or a composition) the claims should include not only the method by which it was determined, e.g. whether by SDS-Page gel electrophoresis, gel filtration or some other method, but also whether the determination was made under denaturing or non-denaturing conditions and whether reducing or non-reducing conditions were are used.

Conclusion

No claims allowed.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER

9/28/05